

REMARKS

Entry of the foregoing, reexamination and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested.

The Office Action Summary indicates that claims 1-10, 12, 22, 26, 40, 42-44, 46, 50, 53, 54, 56, 58 and 63-108 are currently pending in the application. Of these, claims 1-10, 12, 40, 43, 44, 46, 50, 70-84, 88-99, 104 and 105 are indicated as withdrawn from consideration. Claims 22, 26, 42, 53, 54, 56, 58, 63-39, 85-87, 100-103 and 106-108 are indicated as having been considered and rejected.

Applicants would like to correct an apparent typographical error in the response to the Restriction/Election Requirement dated November 3, 2004, which appears to have resulted in claims 88-97 being improperly withdrawn from consideration. Applicants elected with traverse the claims of Group II, which was mistakenly listed as including claims 22, 26, 42, 53, 54, 56, 85-87, 100-103 and 106-108 in the November 3, 2004 Reply. In fact, the restriction requirement indicated that Group II consisted of claims 22, 26, 42, 53, 54, 56, 85-97, 100-103 and 106-108, consistent with a division between methods and compositions.

Apparently following Applicants' typographical error, the Examiner indicated in the Office Action of March 11, 2005 that claims 1-10, 12, 40, 43, 44, 46, 50, 70-84, 88-99, 104 and 105 were withdrawn from consideration, and the error has been perpetuated to this date.

It is respectfully requested that this error be corrected so that the claims withdrawn from consideration are properly recognized to be claims 1-10, 12, 40, 43, 44, 46, 50, 70-84, 98-99, 104 and 105 consistent with the actual restriction requirement. It is requested that claims 88-97 be considered together with the other claims directed to the elected invention as part of the reexamination and reconsideration of the application.

By the present amendment, pending claims 1-2, 4, 22, 43-44, 53-54, 63-64, 66-67, 70-71, 73, 81-82, 85, 87- 88, 91-92, 94-95, 98-99 and 101-108 have been amended.

Support for recitation of “95% sequence identity” can be found in the application as filed, at least on page 21, line 4 and line 23. Support for the recitation of “identical” sequences can be found in the application as filed, at least on page 21. Additional amendments provide more uniform language throughout the claims.

No prohibited new matter has been introduced by way of the above amendments. Applicants reserve the right to file a continuation or divisional application on any subject matter that may have been canceled by way of this Amendment.

Rejections under 35 U.S.C. § 103

The rejection of claims 22, 26, 42, 53, 54, 56, 58, 63-69, 85-87, 100-103, 106-108 under 35 U.S.C. § 103 as allegedly unpatentable over Fire et al. in view of Brown et al. and Lusky et al., the combination in view of Baracchini et al. has been maintained for the reasons of record. The rejection is respectfully traversed for the reasons presented in the Reply filed September 12, 2005 and for the reasons set forth below, which are directed more particularly to the reasons alleged for maintaining the rejection.

Applicants maintain that the prior art fails to establish a proper prima facie case of obviousness. To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. M.P.E.P. § 2143.

It is impermissible to first ascertain factually what applicants did and then view the prior art in such a manner as to select from the random facts of that art only those which may be modified and then utilized to reconstruct applicant's invention from such prior art. *See, e.g., Interconnect Planning Corp. v. Feil*, 227 U.S.P.Q. 543, 550 (Fed. Cir. 1985); *see also, In re Shuman*, 150 U.S.P.Q. 54, 57 (C.C.P.A. 1966). In asserting this rejection, the Office has taken a primary reference that is directed to distinct subject matter, and using impermissible hindsight, selectively picked secondary references that are purported to teach one individual modification or another in an attempt to reconstruct the presently claimed invention.

The only motivation that the Office has alleged, without identifying any particular suggestion in the art underlying the alleged motivation, is a general motivation to increase expression of the constructs allegedly taught in the primary reference. Such a general motivation, if it existed, could have led a person of ordinary skill in the art to any number of alternative modifications of the teachings of the primary reference. However, although any of several alternative modifications of the primary reference might have produced increased expression of the construct, there is no evidence that any of these alternatives would have produced the results obtainable by the present invention, and no reason has been adduced for choosing the presently claimed combination from among the alternative approaches available to the person of ordinary skill in the art.

An analysis of obviousness of a claimed combination must include consideration of the results achieved by that combination. *The Gillette Co. v. S.C. Johnson & Son Inc.*, 16 USPQ2d 1923, 1928 (Fed. Cir. 1990). Critical to the analysis is an understanding of the particular results achieved by the new combination. *Id.* (citing *Interconnect Planning Corporation v. Feil*, 227 U.S.P.Q. 543, 551 (Fed. Cir. 1985)).

In the present Office Action, the Office has alleged that “Combining the seminal teachings provided by Fire, concerning dsRNA mediated inhibition of target gene expression, with the teachings of Brown concerning the routine incorporation of intronic sequences for enhancing gene expression and recombinant gene stability in plants, along with the teachings provided by Lusky concerning the routine incorporation of expression elements into recombinant expression vectors, render the instant invention obvious.” and that “one of ordinary skill in the art would have expected, therefore that the incorporation of intronic sequences into expression vectors encoding the RNAi molecules originally taught by Fire would provide for enhanced stability of expression constructs and would provide for enhanced expression of the RNAi constructs encoded by these expression constructs.”

However, the Office has not identified any teaching in the prior art that would suggest that a person of ordinary skill in the art would have appreciated that there was a problem that required a solution provided by the presently claimed combination. The Office has never adduced any reason why the person of ordinary skill in the art would have expected that enhanced expression of the RNAi encoded by these expression constructs would have lead to an increased reduction of the expression of the target gene. And the Office has not identified any reason that a person of ordinary skill in the art would have viewed either increased expression of the RNAi constructs or increased reduction of the expression of the target gene as necessary. In other words, the Examiner has not provided any particular incentive or motivation for the person of ordinary skill in the art to even try to increase the expression of the RNAi constructs allegedly taught by Fire.

There is no suggestion provided in the cited references why a person skilled in the art seeking to improve the level of reduction in expression of the transgene would have turned to methods for increasing the expression of the RNAi constructs. Indeed, other than a vague

suggestion in Fire that the RNA molecules described therein may be synthesized in vivo, and that endogenous RNA polymerase may mediate such transcription from a transgene in vivo, no further information is provided in Fire. Certainly, Fire does not suggest any correlation between the level of expression of a transgene encoding a dsRNA molecule and the level of reduction in expression of the transgene. Neither do any of the secondary references teach such a correlation. In the absence of any such teaching, the allegation by the Office that one skilled in the art would be motivated to modify the primary reference as proposed is merely a supposition unsupported by any evidence that is insufficient to maintain the present rejection.

Furthermore, the Office will recognize that there are many ways, other than insertion of an intron, to increase expression of any construct, but increased expression of the present RNAi constructs does not account for the increased suppression of a target gene that can be provided by the present invention. Therefore, simply for the sake of argument, if a person of ordinary skill was motivated to increase expression of the construct as the Office proposes, that person could have tried any other method of increasing expression without obtaining the results provided by the present invention.

It is respectfully reiterated that the target gene reduction enhancing effect associated with the inclusion of an intronic sequence is not even correlated to increased expression of the RNAi constructs. Rather, as indicated by Smith et al. 2000 (see response to previous office action) the presence of an intron enhances silencing efficiency by either increased formation of duplex RNA during the process of intron excision from the construct by the spliceosome due to better alignment of the complementary arms of the hairpin in an environment favouring RNA hybridization, or by increased retention of hairpin RNA in the nucleus, or by creation of a smaller, less nuclease-sensitive loop.

Moreover, the person skilled in the art would certainly never have arrived at the currently claimed chimeric genes where the intronic sequence is located between the sense and antisense region as recited in claims 56, 58, 64, 68, 69 and 86.

Even assuming simply for the sake of argument that a person would have been motivated to include an intronic sequence in an RNAi construct as allegedly taught by Fire to obtain increased expression of the construct as alleged by the Office. The person skilled in the art would have included such intronic sequence into the 5' untranslated leader of such chimeric constructs as taught by Brown. Brown clearly teaches “[T]o achieve higher expression in monocot plants. The improvement of the invention comprises expressing a chimeric plant gene with an intron derived from the 70 Kd maize heat shock protein (HSP70) . . . in the **non-translated leader positioned 3' from the gene promoter and 5' from the structural DNA sequencing encoding a protein.**” See, Brown, Summary of Invention. Kelton et al. (cited by the Office) teaches that increased expression is obtained “*only when an intron was included the 5' untranslated region of the FSH receptor transcription unit.*” Kelton et al., Abstract.

For at least the foregoing reasons, the allegations of the Office do not support a prima facie case of obviousness with respect to any of the present claims, and certainly not with respect to claims 56, 58, 64, 68, 69 and 86. Withdrawal of the rejection is respectfully requested.

Claim objections

Claims 22, 40, 43, 44, 53, 54, 64, 66, 67, 71, 81, 82, 85, 87, 88, 92, 94, 95, 99, 100, 103, 105, 106 and 108 have been objected to because of a perceived inconsistency in these claims when describing the extent of sequence identity encompassed by the nucleic acid

constructs. Without agreeing to the basis of the rejection, by the present amendment, the claims have been amended for increased uniformity in language. Withdrawal of the objection is respectfully requested.

Rejections under 35 U.S.C. § 112

Claims 22, 26, 42, 53, 54, 56, 58, 63-69, 85-87, 100-103, 106-108 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that fails to comply with the written description requirement.

In particular, the Office has alleged that the specification does not adequately describe the genus of chimeric DNA that, when transcribed, yields RNA comprising a region that forms an artificial hairpin with a sense strand comprising at least 10, 20 or 50 consecutive nucleotides that are *essentially similar to or having between about 75% to about 100% sequence identity with* the consecutive sequences of a target gene. *See*, OFFICE ACTION at 6 (Emphasis is as indicated by the Office). The rejection is respectfully traversed.

First, Applicants respectfully point out that claims 22, 26, 42, 53, 54, 56, 58, 63-69 were previously rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement (*See*, OFFICE ACTION mailed June 16, 2002 pages 3 to 5). The claims rejected at that time comprised the claim features that the Office has cited present in all of the currently rejected claims. Applicants successfully traversed the rejection on January 16, 2003. The Office indicated that the rejections of record under 35 U.S.C. § 112, first and second paragraphs, had been withdrawn in response to Applicants' amendments and arguments in the next Office Action mailed September 4, 2003. The Office then alleged new grounds of rejection that no longer included a written description rejection. Now, after more than three years, Applicants are faced with having to traverse the same rejection again!

Applicants respectfully submit that the claims as presented are adequately supported by the disclosure. As to the breadth of the claimed genus, this is not a case where the function of an enzyme relies upon the tertiary structure so that a 75% variance of sequence might encompass species that not having a recited function. Rather, this is a case in which the functional utility of the claimed constructs clearly permits a range of similarity to a target sequence. The recited degree of similarity to a target gene is within a range that reasonably correlates with the function of the present constructs. Moreover, it is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention. *Capon v. Eshhar*, 76 U.S.P.Q.2d 1078, 1085 (Fed. Cir. 2005)(citing *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214 (CCPA 1976)).

The Office notes the several examples that are provided in the specification and asserts that the claimed genus is highly variant. Indeed, the examples provide evidence of the general applicability of the invention and breadth of utility provided by the disclosure. Combining the teaching of the specification with the knowledge available in the art of many potential target genes, a person of ordinary skill would have appreciated that the invention encompassed any species of the claimed genus of chimeric constructs that have the recited structural features and sequence similarities to any target gene. It is certainly not practical or necessary for applicants to list every known sequence that could be used in making a construct according to the claimed invention. See, *Capon v. Eshhar*, 76 U.S.P.Q.2d 1078, 1085-86 (Fed. Cir. 2005). The applicants have provided not only general teachings of how to select and recombine DNA, but also specific examples of the production of the claimed chimeric genes. In a case such as this, that is a written description sufficient to support the generic claims. *Id.*

Nevertheless, solely in an effort to expedite the prosecution, and not in anyway acquiescing to the Examiner's rejection, Applicants have amended claims 63, 102 and 107 to replace "essentially similar" with "which is identical". Claims 22, 26, 42, 53, 54, 56, 58, 64-69, 85-87, 100-101, 103, 106 and 108 have been amended to replace "having between about 75 and about 100% sequence identity" with "having between 95% and 100% sequence identity". Corresponding amendments have been made to the withdrawn method claims as well as to product claims 88, 91, 94 and 95.

For at least the foregoing reasons, the withdrawal of the rejection is appropriate and is respectfully requested.

CONCLUSION

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned concerning such questions so that prosecution of this application may be expedited.

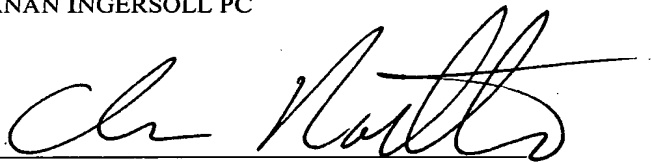
The Director is hereby authorized to charge any appropriate fees that may be required by this paper, and to credit any overpayment, to Deposit Account No. 02-4800.

Respectfully submitted,

BUCHANAN INGERSOLL PC

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